



# The Clinical Course of Rheumatoid Arthritis in Kazakhstani Patients

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## Abstract

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**BACKGROUND:** Rheumatoid arthritis (RA) prevalence according to the worldwide epidemiological data varies from 0.4% to 1.3%. The disability and mortality rate in RA is high. RA clinic is various, and compiles from articular and systemic manifestations.

**AIM:** The aim of our study was to investigate the clinical course of RA in Kazakhstani patients living in North region of our country.

**METHODS:** The 81 women at the age of 30–55 years with a verified diagnosis of RA who have lived in Kazakhstan for at least 10 years were recruited to the study. All participants were examined by the rheumatologist and a standard laboratory examination was carried out. Statistical analysis was conducted in IBM SPSS Statistics 26 software (IBM, USA;1).

**RESULTS:** The statistically significant higher frequency of erosive radiological stages, bone ankylosis ( $\chi^2 = 18.070$  df = 6 p = 0.005) was found in seropositive (rheumatoid factor [RF]+) anti-citrullinated protein/peptide antibody positive (ACPA+) subgroup. The correlation analysis showed strong association between certain RA form activity and inflammatory markers, as well as disease triggers. The discriminant model which predicts the stage of radiological damage was obtained. The sensitivity of model in predicting X-ray Stage I-71.6%, Stage II-29.4%, Stage III-37.5%, and Stage IV-63.6%.

**CONCLUSION:** The debut of the RA on average occurred in the third decade of the patients' life. The joint syndrome had a more unfavorable character RF+ACPA+ patients' subgroup; however, RF+ACPA-negative (ACPA-) subgroup also showed a predisposition to poorer prognosis. The obtained discriminant model may be useful for RA patients' management.

## Introduction

Rheumatoid arthritis (RA) prevalence according to the worldwide epidemiological data varies from 0.4% to 1.3% [1], [2]. The women are more affected to this disease, especially in reproductive age [3], [4]. The ratio of female to male persons is 4:1 [5], [6].

The disability and mortality rate is high in patients with RA compared to general population [7], [8], [9]. According to Sokka *et al.*, there was increase in mortality rate of RA of 1, 5 times [9].

RA clinic is various, and compiles from articular and systemic manifestations. Synovitis, as main culprit, leads to articular destruction and early disability and even premature death. Any joint may be involved to pathological process, leading to the main RA clinical symptom as symmetric polyarthritis [10], which, in turn, leads to joint destruction and loss of working ability. Systematic manifestations such as rheumatoid nodules, serositis, vasculitis, neuropathy,

eye lesions, and Sjogren's syndrome also contribute to the disease aggravation and worsen prognosis [11].

The specific autoantibody production, such as rheumatoid factor (RF) and anti-citrullinated protein/peptide antibody (ACPA), occupy one of the key niches in the disease development and contribute to disease severity. RF and ACPA positivity is associated with early bone destruction and development of RA complications [12], [13], and also contribute to activity increase by DAS28, X-ray stage progression, and low possibility of remission [14], [15].

Environmental and genetic factors play a key role in disease formation. Smoking significantly increases the risk of RA development and takes a dominant place in RA pathogenetic.

Smoking is the most studied environmental risk factor and it doubles risk of RA development [16]. There are several environmental factors include alcohol intake, Vitamin D intake, oral contraceptive use, high birth weight, breastfeeding duration, educational

level, dietary habits, and even low socioeconomic status that potentially may play a particular role in RA development [16], [17], [18].

We initiated the study of RA clinic among Kazakhstani patients to obtain the data on peculiarities of disease course in our population.

## Methods

The 81 women at the age of 30–55 years with a verified diagnosis of RA who have lived in Kazakhstan for at least 10 years were recruited to the study. The study was conducted in accordance with the Helsinki Declaration and was approved by the local ethics committee of Nazarbayev University.

All women included in the study were examined by a rheumatologist in compliance with infectious safety measures in the context of the COVID-19 epidemic. The data were entered into the individual cards of the studied patients.

Collecting anamnesis of the disease, data on the onset of the disease were taken into account, including the nature of the lesion of the joint syndrome at the onset of the disease, the age of the patient at the time of RA manifestation, the duration of the disease, the subjective relationship of the disease with any endogenous or exogenous trigger, and the period from the onset of the disease to the diagnosis of RA.

The collection of clinical data was based on the results of an objective examination of patients by a rheumatologist, as well as by collecting complaints, anamnesis of the disease, and life mentioned earlier. Physical examination was carried out with the determination of the assessment of consciousness, examination of the skin, visible mucous membranes, palpation of peripheral lymph nodes, assessment of the state of muscle tissue, as well as anthropometric data, calculation of body mass index by the method of Kettle, measurement of blood pressure, heart rate, borderline personality disorder, and body temperature. The organs and systems were examined by palpation, percussion, and auscultation. The examination of the musculoskeletal system was carried out according to generally accepted rules. The tender joint count (TJC) and swollen (SJC) large and small joints count were obtained. The symptoms of transverse compression of the hands and feet, the strength of the compression of the hands were evaluated. The individual chart showed the involvement of the proximal and distal interphalangeal joints of the thumbs and other small joints with deformity and defiguration in the pathological process. Data on extra-articular manifestations of the disease and the development of complications were recorded. Pain was assessed by both the patient and

the doctor using a visually analog pain scale (VAS), and the overall average score was analyzed. The disease activity was assessed according to the DAS-28 disease activity index in RA. The X-ray stage was assessed according to the X-ray images for the last year. Functional status stratified according to ability to perform usual activities of daily living (self-care, professional and non-professional).

All patients underwent laboratory testing in the clinical and diagnostic laboratory. Blood sampling was carried out strictly on an empty stomach, after a 12–14 h period of fasting, in compliance with infectious safety measures. All patients underwent general clinical methods of research with the determination of indicators of the general blood test: The content of hemoglobin, red blood cells, platelets, leukocyte formula, and the erythrocyte sedimentation rate according to Panchenkov and Westergren; and the determination of the indicators of the general urinalysis. Biochemical blood tests determined the levels of alanine aminotransferase, aspartate aminotransferase, total protein, protein fractions, creatinine, cholesterol, glucose, and C-reactive protein (CRP). Immunological parameters such as RF, ACPA, antibodies to SS-A (Ro), and SS-B (La) components were also determined. ACPA and RF were measured with a second-generation enzyme-linked immunosorbent assay.

Statistical analysis of the data was carried out according to the generally accepted standards in the program IBM SPSS Statistics 26 software (IBM.USA;1).

## Results

The study group included 81 women diagnosed with RA aged 30–55 years, Me=43.98 95% CI (43–45).

About 75.3% (n = 61) of the women studied had a seropositive (RF+) variant of the course of RA, while 24.3% (n = 20) had a seronegative (RF-) one, while 70.7% (n = 58) had an ACPA-positive (ACPA+) variant and 28% (n = 23) ACPA-negative (ACPA-) variant of the disease course, in connection with which a comparative analysis was conducted between the RF+ACPA+, RF+ACPA-, and RF - ACPA+ subgroups (Table 1).

**Table 1: Distribution of subjects in subgroups**

| Variables           | RF+ ACPA+n = 38 |         | RF+ACPA-n=23 |         | RF- ACPA+n = 20 |         |
|---------------------|-----------------|---------|--------------|---------|-----------------|---------|
|                     | Me/n            | Q1-Q3/% | Me/n         | Q1-Q3/% | Me/n            | Q1-Q3/% |
| Age, years          | 43.5            | 37.5-51 | 44           | 31-50   | 47              | 39-51   |
| Kazakh ethnic group | 35              | 92.1%   | 20           | 87%     | 16              | 80%     |
| Slavic ethnic group | 3               | 7.9%    | 3            | 13%     | 4               | 20%     |

The comparative analysis showed that the frequency of disease triggers had equal proportions both in the seropositive course of the disease and in the seronegative course.

The study of the disease debut in the studied subgroups showed no statistically significant differences.

However, it should be noted that the median age of disease onset in the RF - ACPA+ group was 40.5 years, which is relatively higher than in the seropositive subgroups (Figure 1 for all indicators p > 0.05).

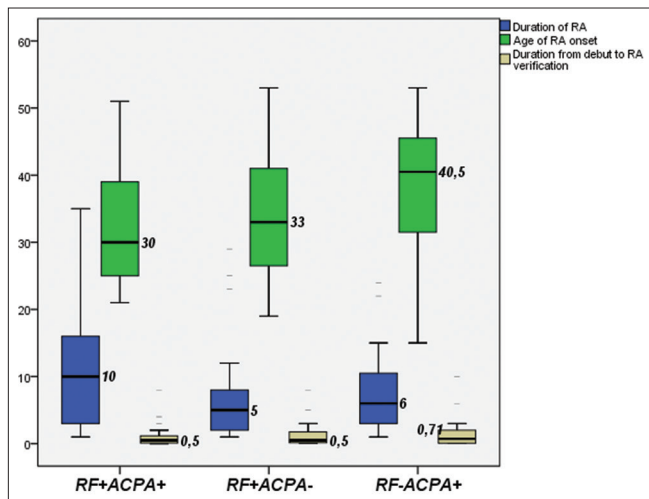


Figure 1: Comparative analysis of the disease debut in the studied subgroups

Further, a comparative analysis of the clinical course of the disease was carried out, which showed a predominance of the articular form in all the studied subgroups. At the same time, the proportion of symmetrical joint lesions did not differ statistically and accounted for 80.6%, 73.9%, and 68.4%, respectively, but women with RF+ACPA+ course of the disease had a significantly higher incidence of late-stage disease 39.5%, 8.7%, and 5%, respectively,  $\chi^2 = 12.410$  df = 2 p = 0.002 (Table 2).

Table 2: Clinical data of RA in the studied subgroups

| Variables              | RF+ACPA+, n = 38<br>n (%) / Me (Q1-Q3) | RF+ACPA-, n = 23 | RF-ACPA+, n = 20 |
|------------------------|--|------------------|------------------|
| Expanded stage of RA   | 23 (60.5%)                             | 21 (91.3%)       | 19 (95%)         |
| Late stage of RA       | 15 (39.5%)                             | 2 (8.14%)        | 1 (5%)           |
| Joint syndrome         | 38 (100%)                              | 22 (95.7%)       | 19 (95%)         |
| Symmetrical arthritis  | 29 (80.6%)                             | 17 (73.9%)       | 13 (68.4%)       |
| Asymmetrical arthritis | 9 (19.4%)                              | 6 (26.1%)        | 7 (31.6%)        |
| TJC                    | 7 (2-4.5)                              | 6 (2-13)         | 7 (4-13.5)       |
| SJC                    | 3 (1-9.5)                              | 2 (0-8)          | 2.5 (0-5.75)     |
| VAS                    | 5 (3-7)                                | 5 (3-7)          | 5 (3-7)          |
| DAS28                  | 4.59 (3.8-6.2)                         | 4.5 (3.7-5.4)    | 4.28 (3.2-5.6)   |
| Disease activity       | 2 (2-3)                                | 2 (2-3)          | 2 (2-3)          |

TJC: Tender joint count, SJC: Swollen joint count, VAS: Visually analog scale.

The comparative analysis of the disease activity in terms of TJC, SJC, VAS, and DAS 28 also showed no statistically significant differences (Table 2; for all indicators p > 0.05), thus the course of the disease among the studied individuals with the seropositive form did not have such clinical differences with the seronegative form of the disease, which was reflected in the frequency of involvement in the pathological process of large and small joints (Figure 2).

However, a profound study of the joint syndrome in the studied subgroups showed that individuals with RF+ACPA+ course of the disease with a statistically significant higher frequency had erosive radiological stages of the disease up to the development of bone ankylosis ( $\chi^2 = 18.070$  df = 6 p = 0.005) with pronounced deformity (Somers d=0.300 p=0.008) and impaired joint function of functional Classes 3 and 4 (Table 3).

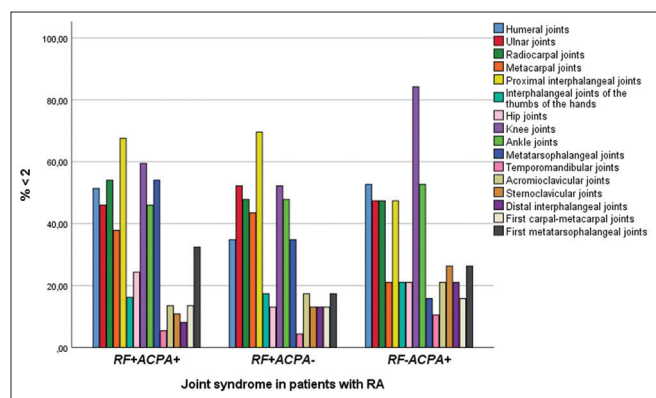


Figure 2: Joints involved in the pathological process in the studied subgroups

Further, the analysis of laboratory indicators of the inflammatory process activity was carried out, which revealed the presence of statistically significant differences in the study groups, which are shown in Figure 3.

Table 3: X-ray stage, functional status, and the presence of joint deformity in the studied subgroups

| Variables                   | RF+ACPA+, n = 38<br>N (%) | RF+ACPA-, n = 23 | RF-ACPA+, n = 20 |
|-----------------------------|---------------------------|------------------|------------------|
| X-ray Stage I               | 6 (15.8%)                 | 5 (21.7%)        | 7 (35%)          |
| X-ray Stage II              | 10 (26.3%)                | 12 (52.2%)       | 12 (60%)         |
| X-ray Stage III             | 12 (31.6%)                | 5 (21.7%)        | 1 (5%)           |
| X-ray Stage IV              | 10 (26.3%)                | 1 (4.4%)         | 0                |
| Functional status I         | 7 (18.4%)                 | 10 (43.5%)       | 6 (30%)          |
| Functional status II        | 23 (60.5%)                | 11 (47.8%)       | 14 (70%)         |
| Functional status III       | 7 (18.4%)                 | 3 (8.7%)         | 0                |
| Functional status IV        | 1 (2.7%)                  | 0                | 0                |
| Presence of joint deformity | 23 (60.5%)                | 11 (47.8%)       | 5 (25%)          |

Thus, it was found that in the RF+ACPA+ subgroup of the course of the disease, the higher values of the level of CRP (p = 0.026) and alpha-1 globulins (p = 0.003) were observed, confirming the acute inflammatory process, which was also reflected in the direct correlation (Table 4) of the different strength of these indicators with the level of TJC, SJC, and VAS, duration of the course of RA and DAS 28 points.

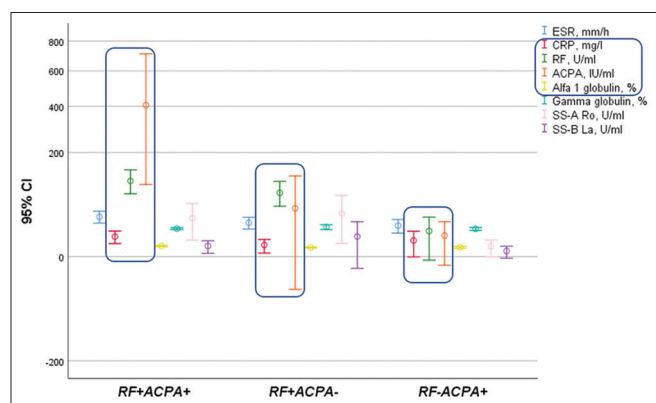


Figure 3: Comparative analysis of laboratory parameters

Correlation analysis in the RF+ ACPA- group showed a large association of disease activity with

Table 4: Correlation analysis in the RF+ACPA+ subgroup

| RF+ ACPA+          | TJC   | SJC   | VAS by patient | VAS by doctor | RA duration | DAS 28 |
|--------------------|-------|-------|----------------|---------------|-------------|--------|
| CRP, mg/l          |       |       |                |               |             |        |
| $\rho$             | 0.561 | 0.559 | 0.385          | 0.459         | 0.447       | 0.748  |
| p                  | 0.000 | 0.000 | 0.020          | 0.005         | 0.006       | 0.000  |
| Alfa 1 globulin, % |       |       |                |               |             |        |
| $\rho$             |       | 0.476 | 0.431          | 0.428         |             | 0.552  |
| p                  |       | 0.006 | 0.014          | 0.014         |             | 0.001  |

TJC: Tender joint count, SJC: Swollen joint count, VAS: Visually analog scale, CRP: C-reactive protein.

markers of autoimmune inflammation-Gamma globulins, antibodies to Robert and Lane components (Table 5).

While in the group with a seronegative course of RA, relationships with disease triggers, such as the number of pregnancies and the duration of breastfeeding, were revealed, which confirm a more favorable course and late onset of RA among women with more pregnancies and longer duration of breastfeeding (Table 6).

Further, on the basis of the obtained results, a multinomial discriminant analysis was performed to predict such an endpoint as the stage of radiological damage to the joints. Quantitative variables were selected as independent factors, such as the age of the women studied at the time of examination, the age of disease onset, the duration of RA, SJC, TJC, the patient's and doctor's VAS, DAS 28 scores, the number of pregnancies and births, as well as the duration of breast-feeding in the anamnesis, as well as laboratory indicators of disease activity. As a result of the discriminant analysis performed using the step selection method, a discriminant model was obtained at step 2 (Figure 4), which is a system of equations (1) and (2):

$$F1 = -1,635 + 0,037 * X_{CRP} + 0,144 * X_{RA\text{duration}} \quad (1)$$

$$F2 = 0,117 + 0,071 * X_{CRP} - 0,078 * X_{RA\text{duration}} \quad (2)$$

where

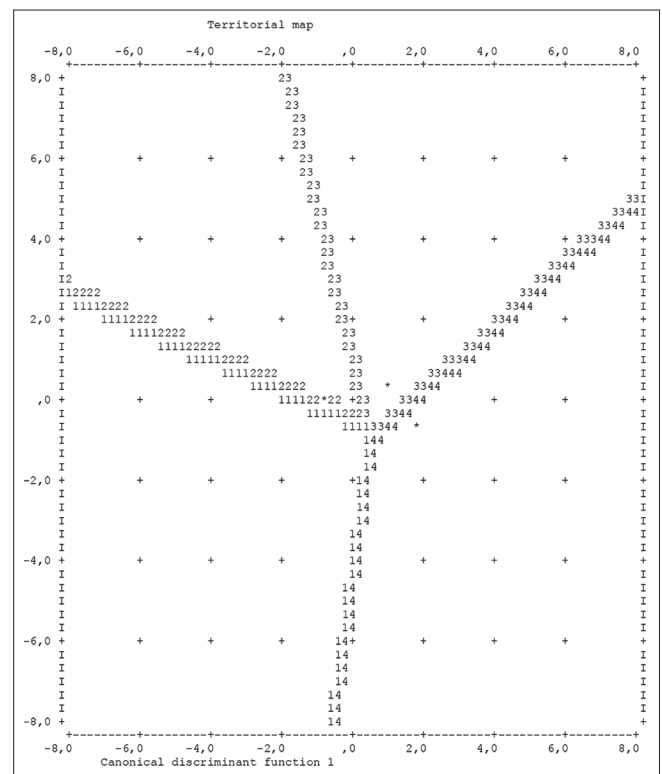
- F1 - is the value of the discriminant function 1;
- F2 - the value of the discriminant function 2;
- $X_{CRP}$  – CRP (mg/l);
- $X_{RA\text{duration}}$  - duration of RA (years)

Thus, the obtained discriminant model allows us to predict the stage of radiological damage of the joint calculating the coordinates of the functions F1 and F2 on the territorial map, where the predicted stage will be at the intersection of the x and y axes. The sensitivity of the obtained model (including after cross-checking) predicting the first radiological stage of RA was 71.6%, Stage II-29.4%, Stage III-37.5%, and Stage IV-63.6%.

**Table 5: Correlation analysis in the RF+ACPA- subgroup**

| RF+ ACPA-         | TJC   | SJC   | VAS by patient | VAS by doctor | RA duration | Age of RA debut | Time from debut to RA diagnosis | DAS 28 |
|-------------------|-------|-------|----------------|---------------|-------------|-----------------|---------------------------------|--------|
| ESR, mm/h         |       |       |                |               |             |                 |                                 |        |
| ρ                 | 0.437 | 0.447 | 0.416          | 0.429         |             |                 |                                 | 0.729  |
| p                 | 0.037 | 0.033 | 0.048          | 0.041         |             |                 |                                 | 0.000  |
| Gamma globulin, % |       |       |                |               |             |                 |                                 |        |
| ρ                 | 0.635 | 0.527 | 0.532          | 0.545         | -0.478      | 0.633           | -0.410                          | 0.666  |
| p                 | 0.003 | 0.020 | 0.019          | 0.016         | 0.039       | 0.004           | 0.081                           | 0.002  |
| SS-A Ro           |       |       |                |               |             |                 |                                 |        |
| ρ                 | 0.544 | 0.370 | 0.444          | 0.458         |             | 0.590           |                                 | 0.481  |
| p                 | 0.009 | 0.090 | 0.039          | 0.032         |             | 0.004           |                                 | 0.023  |
| SS-B La           |       |       |                |               |             |                 |                                 |        |
| ρ                 | 0.530 | 0.452 |                | 0.501         | -0.436      | 0.455           |                                 | 0.461  |
| p                 | 0.011 | 0.035 |                | 0.018         | 0.042       | 0.034           |                                 | 0.031  |

TJC: Tender joint count, SJC: Swollen joint count, VAS: Visually analog scale, ESR: Erythrocyte sedimentation rate.



**Figure 4: Territorial map of the multinomial discriminant analysis of the X-ray stage**

## Discussion

This is the first study of RA clinical course in Kazakhstan, which can be useful and supplement the data on the RA study in the world. In the group under the study, the RF+ACPA+ disease form prevailed, which is consistent with the data of many studies [1], [4], [19], [20], [21], [22]. The median age of disease onset was in the third decade of life, which also corresponds to the results of the majority of studies [4], [11], [23], [24], [25], [26], [27], [28], however, in Japan a later onset of RA was observed [29]. Studying the clinical picture of RA in our sample, the predominance of the articular form in all studied subgroups was found. Women with RF+ACPA+ course of the disease had a

**Table 6: Correlation analysis in the RF- ACPA+ subgroup**

| RF- ACPA+                  | Age of RA debut | DAS 28 |
|----------------------------|-----------------|--------|
| Number of pregnancies      |                 |        |
| ρ                          |                 | -0.434 |
| p                          |                 | 0.056  |
| Duration of breast-feeding |                 |        |
| ρ                          | 0.549           |        |
| p                          | 0.015           |        |

significantly higher incidence of late-stage disease and this subgroup also had erosive radiological stages of the disease up to the development of bone ankylosis with severe deformities and impaired joint function of functional Classes 3 and 4 with a statistically significant higher frequency, these data confirm a more severe course of RF+ ACPA+ RA form. These results support and supplement the data on a poorer prognosis of seropositive and ACPA-positive RA form [14], [30], [31], [32], [33]. It was found that in the RF+ACPA + subgroup of the course of the disease, the higher values of the level of CRP ( $p = 0.026$ ) and alpha-1 globulins ( $p = 0.003$ ) were observed, which supports the above-mentioned data. The seropositive (RF+) ACPA- negative (ACPA-) subgroup of our study showed a large association of disease activity with markers of autoimmune inflammation, such as Gamma globulins, and antibodies to Robert and Lane components, which, in turn, also indicates a more severe course and a worse prognosis of RA in this group, particularly there should be alertness about Sjogren syndrome. The last mentioned results can be explained by the study of Hiwa *et al.*, who came to the conclusion that RF-positive subset of ACPA-negative RA may convert to ACPA-positive form of the disease [34]. Studying the RA triggers, we have obtained the data, which indicates the more favorable course and late onset of RA among women with more pregnancies and longer duration of breastfeeding, which may be consistent with the data of number of authors, who studied protective role of the breastfeeding in RA development [35], [36], [37], [38]. Concerning the number of pregnancies Chen *et al.* did not find any relationship between the number of pregnancies and RA risk in their study [39]; however, Ren *et al.* indicated the strong relationship of the number of parity and decreased risk of RA [40]. The discriminant model, that allows to predict radiological damage using only two quite affordable parameters, may be applicable in RA patients' management.

## Conclusion

The debut of the RA on average occurred in the third decade of the patients' life. The joint syndrome had a more unfavorable character in RF+ACPA+ patients' subgroup, however, RF+ACPA- subgroup also showed a predisposition to poorer prognosis. The obtained discriminant model may be useful for RA patients'

management. Further studies on larger cohorts are needed to expand our obtained results.

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